CLAIMS

We claim:

1. A fusion protein comprising a first protease inhibitor comprising alpha 1-antitrypsin or a functionally active portion thereof, and a second protease inhibitor or a functionally active portion thereof.

2. A fusion protein comprising alpha 1-antitrypsin or a functionally active portion thereof, and secretory leukocyte protease inhibitor or a functionally active portion thereof.

3. A fusion protein comprising alpha 1-antitrypsin or a functionally active portion thereof, and a tissue inhibitor of metalloproteases or a functionally active portion thereof.

4. The fusion protein of claim 2, comprising

a) amino acids from about 1 to about 394 of alpha 1-antitrypsin; and

b) amino acids from about 1 to about 107 of secretory leukocyte protease inhibitor.

5. A polynucleotide encoding the fusion protein of claim 1, 2, 3, or 4.

6. An expression vector comprising the polynucleotide of claim 5.

7. A host cell comprising the expression vector of claim 6.

8. A pharmaceutical composition comprising the fusion protein of claim 1, 2, 3, or 4 admixed with a pharmaceutically acceptable vehicle.

9. A method of producing the fusion protein of claim 1, 2, 3, or 4, said method comprising culturing a transformed host cell containing an expression vector encoding a fusion protein under conditions appropriate for expressing said fusion protein.

10. The method of claim 9 further comprising purifying said fusion protein.

11. The fusion protein of claim 1 wherein the second protease inhibitor inhibits a serine protease.

12. The fusion protein of claim 1, wherein the second protease inhibitor inhibits a metalloprotease.

13. The fusion protein of claim 1 wherein the second protease inhibitor inhibits an aspartyl protease.

14. The fusion protein of claim 1 wherein the second protease inhibitor inhibits a cysteine protease.

15. The fusion protein of claim 3 wherein the tissue inhibitor of metalloproteases is TIMP-1 or a functionally active portion thereof.

16. The fusion protein of claim 4 wherein the carboxy terminus of amino acids from about 1 to about 394 of alpha 1-antitrypsin is linked to the amino terminus of amino acids from about 1 to about 107 of secretory leukocyte protease inhibitor.

17. The fusion protein of claim 4 wherein the carboxy terminus of amino acids from about 1 to about 107 of secretory leukocyte protease inhibitor is linked to the amino terminus of amino acids from about 1 to about 394 of alpha 1-antitrypsin.

18. The fusion protein of claim 3, comprising

a) amino acids from about 1 to about 394 of alpha 1-antitrypsin; and

b) amino acids from about 1 to about 184 of tissue inhibitor of metalloproteases-1.

19. The fusion protein of claim 18 wherein the carboxy terminus of amino acids from about 1 to about 394 of alpha 1-antitrypsin is linked to the amino terminus of amino acids from about 1 to about 184 of tissue inhibitor of metalloproteases-1.

20. The fusion protein of claim 18 wherein the carboxy terminus of amino acids from about 1 to about 184 of tissue inhibitor of metalloproteases-1 is linked to the amino terminus of amino acids from about 1 to about 394 of alpha 1-antitrypsin.

21. The fusion protein of claim 3 comprising

a) amino acids from about 1 to about 394 of alpha 1-antitrypsin; and

b) amino acids from about 1 to about 126 of tissue inhibitor of metalloproteases-1.

22. The fusion protein of claim 21 wherein the carboxy terminus of amino acids from about 1 to about 394 of alpha 1-antitrypsin is linked to the amino terminus of amino acids from about 1 to about 126 of tissue inhibitor of metalloproteases-1.

23. The fusion protein of claim 21 wherein the carboxy terminus of amino acids from about 1 to about 126 of tissue inhibitor of metalloproteases-1 is linked to the amino terminus of amino acids from about 1 to about 394 of alpha 1-antitrypsin.

24. A fusion protein comprising

a) a polypeptide comprising amino acids from about 1 to about 394 of alpha 1-antitrypsin; and

b) a polypeptide comprising amino acids from about 1 to 127 of tissue inhibitor of metalloproteases-1,

wherein the alpha 1-antitrypsin polypeptide is covalently linked to the tissue inhibitor of metalloproteases-1 polypeptide through a disulfide bond between amino acid 127 of the tissue inhibitor of metalloproteases-1 polypeptide and a free cysteine residue of the alpha 1-antitrypsin polypeptide.

25. The fusion protein of claim 24 wherein the free cysteine residue of the alpha 1-antitrypsin polypeptide is at position 232 in SEQ ID NO: 2.

26. A method for inhibiting protease activity, comprising contacting the protease with the fusion protein of claims 1, 2, 3, or 4.

27. The method of claim 26 wherein the protease activity is associated with a disorder selected from the group consisting of emphysema, asthma, chronic obstructive pulmonary disease, cystic fibrosis, otitis media, and otitis externa.

28. The method of claim 26, wherein the protease activity is associated with HIV infection.

29. The method of claim 26, wherein the fusion protein is contacted with the protease by administering the fusion protein to an individual having the protease.

30. A method of treating an individual suffering from, or at risk for, a disease or disorder involving unwanted protease activity comprising administering to the individual an effective amount of the fusion protein of claims 1, 2, 3, or 4.

31. The method of claim 30, wherein the individual suffers from emphysema.

32. The method of claim 30, wherein the individual suffers from asthma.

33. The method of claim 30, wherein the individual suffers from chronic obstructive pulmonary disease.

34. The method of claim 30, wherein the individual suffers from cystic fibrosis.

35. The method of claim 30, wherein the individual suffers from otitis media or otitis externa.